Title
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Journal
Communicative & integrative biology, 7(1)

ISSN
1942-0889

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Publication Date
2014

DOI
10.4161/cib.28358

Peer reviewed

Communicative & Integrative Biology 7:I, e28358; March; © 2014 Landes Bioscience

PTEN

A master regulator of neuronal structure, function, and plasticity

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Keywords: LTP, PTEN, autism, cortex, development, epilepsy, hippocampus, mTOR, plasticity

PTEN (phosphatase and tensin homolog on chromosome ten) is a dual protein/lipid phosphatase that dephosphorylates PIP3, thereby inhibiting the AKT/mTOR pathway. This inhibition ultimately decreases protein translation, cell proliferation and cell growth. In the central nervous system, inhibition of PTEN leads to increased stem cell proliferation, somatic, dendritic and axonal growth, accelerated spine maturation, diminished synaptic plasticity, and altered intrinsic excitability. In agreement with these findings, patients carrying single-copy inactivating mutations of *PTEN* suffer from autism, macrocephaly, mental retardation, and epilepsy.[1-9] Understanding the mechanisms through which PTEN modulates the structure, function, and plasticity of cortical networks is a major focus of study. Preventing and reversing the changes induced by loss of Pten in model animals will pave the way for treatments in humans.

Role of Pten in Neuron Morphology and Connectivity

PTEN is essential for both, central nervous system (CNS) development and maintenance of CNS circuit structure and function. The generation of conditional mutant animals has allowed exquisite control over temporal and spatial patterns of Pten expression and delineated specific roles for Pten at each developmental stage. During early embryonic development, *Pten* deletion in proliferating neural stem/progenitor cells results in increased cell proliferation, and severe defects in cortical, hippocampal and cerebellar lamination.[10,11] Pten also inhibits cell proliferation of adult born neural stem cells, controlling self-renewal in the olfactory bulb[12] and dentate gyrus.[13] After neurons become post-mitotic, *Pten* deletion or knock-down has dramatic effects on neuronal growth, highlighting the importance of Pten for controlling post-mitotic neuronal development.[14,15] Deletion of *Pten* in differentiated postmitotic cortical and hippocampal neurons leads to progressive somatic and dendritic hypertrophy, and the growth of ectopic dendritic branches.[16] *Pten* deletion also leads to progressive growth of axonal arbors, which is most readily observed in the hippocampal mossy fiber pathway where deletion also leads to enlargement of presynaptic terminals and increased vesicle numbers.[16,17] Indeed, Pten is enriched in the axonal compartment and the growth cones during axonal extension, coupling semaphorins (Sema3A) to growth cone collapse.[18]

The effects of *Pten* deletion on spine density and morphology are more complex and likely depend on neuronal identity and the differences in spine classification. Recent studies in basolateral amygdala and dentate gyrus granule neurons suggest that *Pten* deletion does not change overall dendritic protrusion density, but induces a shift in protrusion morphology from thin spines to mushroom spines.[19] Rapamycin, the mTORC1 inhibitor prevents somatic, dendritic, and axonal growth induced by *Pten* deletion, and reverses some but not all these anatomical abnormalities if rapamycin is administered after these changes have already occurred.[20]

Pten deletion in adult excitatory cortical neurons using α-CaMK2-Cre conditional deletion of floxed-*Pten*, reveals that Pten is not only necessary for proper cortical development, but also exerts profound control over dendritic growth in adulthood. By using two-photon imaging of the same cortical dendritic arbors over weeks, *Chow et al.* show that apical dendrites of L2/3 pyramidal neurons that underwent deletion of *Pten* in adulthood, demonstrate dramatic and progressive growth. Newly elongated dendritic segments form new spines. Importantly, treatment of these mice with the mTORC1 inhibitor, rapamycin, halts dendritic growth, and reduces spine density on the newly grown segments. Adult deletion of *Pten* in L5 neurons has no effects on apical dendritic arbors, suggesting that Pten exerts distinct effects on different cortical layers in adulthood.[21]

These structural changes are accompanied by profound alterations in synaptic function. In the dentate gyrus, consistent with the increase in the proportion of mature dendritic spines, *Pten* knockdown or deletion increases the frequency of excitatory (miniature and spontaneous) postsynaptic currents.[19,22] To dissect the presynaptic and postsynaptic contributions to altered functional connectivity in excitatory and inhibitory neurons, *Weston* and colleagues have carried out studies in autaptic dentate granule cell and striatal cultures. They find that *Pten* deletion increases evoked synaptic release onto both inhibitory and excitatory neurons, mainly by

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Submitted: 01/28/2014; Accepted: 02/25/2014; Published Online: 03/05/2014
Citation: Garcia-Junco-Clemente P, Golshani P. PTEN: A master regulator of neuronal structure, function, and plasticity. Communicative & Integrative Biology 2014; 7:e28358; http://dx.doi.org/10.4161/cib.28358

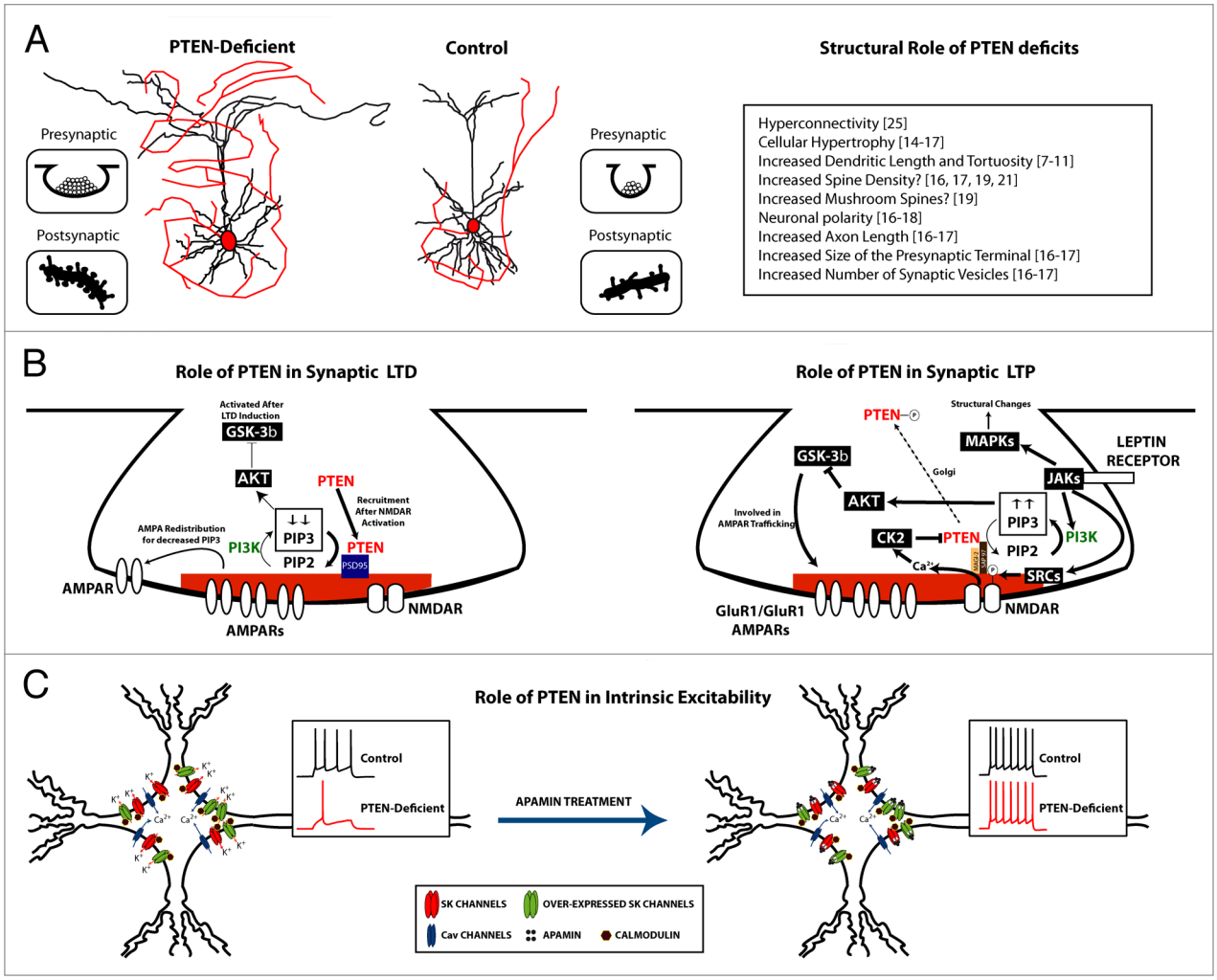

Figure 1. (**A**) Left: A drawing representing dendritic and axonal growth caused by loss of PTEN. Insets: PTEN loss causes increased synaptic vesicles and dendritic protrusions. Right: List of changes in neuronal anatomy caused by loss of PTEN. The numbers are references supporting each finding. (**B**) An illustration demonstrating the potential role of PTEN in synaptic long-term depression (LTD) and long term potentiation (LTP). C. A schematic illustrating that loss of PTEN leads to increased expression of calcium-activated potassium channels and decreased intrinsic excitability which is in turn rescued by treatment with the SK channel blocker, apamin.

increasing the number of vesicles available for release.[23] These effects are counterbalanced by impaired vesicle fusion induced by hyperactive mTOR signaling, although the prevailing overall effect was an increase in functional connectivity. In the dentate gyrus, these physiological changes have dramatic effects on neuronal synchronization, as loss of Pten in as few as 9% of dentate granule cells lead to development of spontaneous seizures.[24] Loss of Pten in auditory cortical neurons enhances the strength of long-range connections inputs from both the contralateral auditory cortex and the thalamus, as well as from local inputs. This hyperconnectivity may constitute a physiological basis for ASD phenotypes associated with problems in processing and integration of complex sensory information.[25]

Pten and Synaptic Plasticity

In addition to changes in basal synaptic transmission, Pten is also intimately involved in the mechanisms underlying synaptic plasticity. Activity-induced long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission are two types of enduring changes in neuronal connections that underlie learning and memory functions.[26] Conditional *alpha-CaMK2-Cre* dependent deletion of *Pten* in mature differentiated CA1 neurons demonstrated that *Pten* deletion leads to deficits in both major forms of synaptic plasticity (LTP and LTD) before the onset of anatomical abnormalities, suggesting that Pten controls structural synaptic growth and synaptic plasticity through independent mechanisms.[27,32] Acute blockade of PI3K impairs LTP in hippocampal CA1 synapses, which reflects the importance of PI3K/Pten balance in synaptic plasticity.[28] The precise mechanism through which Pten controls synaptic plasticity is not completely understood. During LTD, NMDA receptor activation triggers the association between Pten and postsynaptic density-95 (PSD-95). This interaction anchors Pten to the postsynaptic membrane, eventually depressing AMPA receptor-mediated synaptic responses.[29] Pten may also exert effects on LTP through the hormone leptin, which

phosphorylates and inactivates Pten, increasing the membrane expression of GluR1 and thus, the synaptic density of GluR2-lacking AMPA receptors in adult hippocampus.[30,31] In dentate granule cells, conditional *Pten* ablation inhibits metabotropic glutamate receptor (mGluR) and protein synthesis-dependent LTD.[32]

Changes in the structure of the postsynaptic terminal affect synaptic plasticity regulation. Drebrin is a protein highly enriched in dendrites, and modulates synaptic plasticity by affecting the spine morphology and by regulating neuronal transmission.[33] Clustering of Drebrin is regulated by AMPA receptor activity[34] and Drebrin regulates the synaptic targeting of NMDA receptors.[35] PTEN negatively regulates Drebrin phosphorylation, and neuronal activity induces a dissociation of the PTEN/Drebrin complex. The reduced levels of Drebrin observed in patients with Alzheimer's disease suggest an important role of PTEN/Drebrin interaction in synaptic plasticity.[36]

Role of Pten in Intrinsic Excitability

Changes in voltage or calcium-gated conductances which modulate the intrinsic excitability of neurons can sculpt how neuronal networks respond to changes in synaptic weights. These changes can occur at the level of single dendrites,[37] within the somatic compartment, or even in the axon initial segment,[38] and fine tune the way input is integrated, maintaining the dynamic range of the neuron. There is increasing evidence that Pten and mTOR-related proteins can regulate the expression of intrinsic ion channels, modulating the intrinsic excitability of the cell. The first evidence for this modulation was demonstrated in hippocampal neurons where the mTOR inhibitor rapamycin increased dendritic translation of the potassium channel Kv1.1.[39] In the hypothalamus, aging increases mTOR signaling in the pro-opiomelanocortin (POMC), elevating ATP activated potassium (K (ATP)) channel activity, ultimately resulting in obesity.[40] In the cerebellum, neuregulin-1 and neuritin increase the density of Kv4.2 channels by engaging the mTOR pathway.[41,42]

Our own work[43] demonstrates that single-copy loss of *Pten* in the mature visual cortex significantly decreases intrinsic excitability of L2/3 excitatory visual cortical neurons without changing dendritic branching. These neurons demonstrated decreased input resistance and increased amplitude of the spike after hyperpolarization. As calcium activated conductances play a large role in setting the amplitude of the AHP, we tested whether blockade of these conductances could normalize the firing properties and the spike AHP in the *Pten* mutants. Blockade of SK channels (but not BK channels) rescued the intrinsic firing properties and AHP of Pten deficient neurons. In addition, we found an increased protein expression of the SK2 channel subunit in visual cortex. Finally, we asked whether these changes in the intrinsic firing patterns affected the way about how visual information is processed *in vivo*. We found that loss of Pten decreased the magnitude of the visually evoked action potential discharges, without altering the orientation selectivity of the neurons. Therefore, single copy loss of *Pten*, through changes in SK channel expression levels, decreases the responsiveness of excitatory visual cortical neurons. These findings provide additional avenues for research in treating channelopathies induced by *PTEN* mutations.

PTEN and Human Disease

These physiological changes are especially relevant as *de novo* or inherited mutations in *PTEN* are emerging as one of the most validated causes of autism spectrum disorder, intellectual disability and extreme macrocephaly.[1,9] These disorders add to the already well-established role of *PTEN* mutations in causing the PTEN hamartoma tumor syndromes which include Cowden,[44] Bannayan-Riley-Ruvalcaba,[45] Lhermitte Duclos,[44] and Proteus Syndromes.[46] In the future, it will be essential to determine which of the complex structural and physiological changes induced by *PTEN* deficits can be reversed or ameliorated by mTOR inhibition, and which changes will necessitate other interventions to normalize intrinsic excitability, synaptic connectivity, and plasticity.(**Fig.1**)

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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